BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2008.03249.x

Cisapride and ventricular arrhythmia

Sean Hennessy[1], Charles E. Leonard,[1] Craig Newcomb,[1] Stephen E. Kimmel[1,2] & Warren B. Bilker[1]

[1]Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, and Center for Education and Research on Therapeutics, University of Pennsylvania School of Medicine, and [2]Division of Cardiology, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Correspondence
Sean Hennessy, PharmD, PhD, University of Pennsylvania School of Medicine, 423 Guardian Drive/803 Blockley Hall, Philadelphia, PA 19104-6021, USA.
Tel: +1 215 898 9112
Fax: +1 215 573 5315
E-mail: hennessy@mail.med.upenn.edu

Keywords
cardiac arrhythmias, Centers for Medicare and Medicaid Services, cisapride, nested case–control studies, pharmacoepidemiology, sudden cardiac death

Received
19 December 2007

Accepted
9 June 2008

Published *OnlineEarly*
25 July 2008

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Case reports have linked cisapride to ventricular arrhythmia and sudden cardiac death.
- However, two prior epidemiological studies have failed to show an association between cisapride and serious arrhythmia.

WHAT THIS STUDY ADDS

- Overall, cisapride was associated with a doubling to tripling of the risk of hospitalization for sudden cardiac death and ventricular arrhythmia, and a near eightfold risk in the initial prescription period.
- Although potentially arrhythmogenic CYP3A4 inhibitors were associated with an increased risk in cisapride users, this appears to be due to a direct effect of the drugs themselves rather than an interaction with cisapride.

AIMS

We aimed to examine the association between cisapride and ventricular arrhythmia, and examine the relationship to dose and CYP3A4 inhibitors.

METHODS

A nested case–control study was conducted in Medicaid beneficiaries exposed to cisapride, metoclopramide or a proton pump inhibitor (PPI) from 1999 to 2000. Cases were hospitalized with a principal International Classification of Diseases-9 code indicating sudden cardiac death or ventricular arrhythmia. Controls had at least as much event-free person time following the study prescription as its matched case.

RESULTS

A total of 145 cases and 7250 controls were identified. The unadjusted rate ratio for cisapride *vs.* PPIs was 1.49 (95% confidence interval 0.96, 2.25). The adjusted odds ratio (OR) for cisapride *vs.* PPIs was 2.10 (1.34, 3.28). Excluding persons in managed care, the adjusted OR for cisapride was 2.92 (1.55, 5.49). In the initial prescription period, the adjusted OR for cisapride *vs.* PPIs was 7.85 (1.95, 31.60). Non-arrhythmogenic CYP3A4 inhibitors were not associated with an increased risk in users of cisapride or PPI inhibitors. The OR for potentially arrhythmogenic CYP3A4 inhibitors was 3.79 (1.76, 8.15) in cisapride users and 3.47 (2.06, 5.83) in PPI users.

CONCLUSIONS

Cisapride was associated with a doubling to tripling of the risk of hospitalization for ventricular arrhythmia, and a nearly eightfold risk in the initial prescription period. Although use of potentially arrhythmogenic CYP3A4 inhibitors was associated with an increased risk, this appears to be due to a direct effect of the drugs themselves rather than an interaction with cisapride.

Introduction

Cisapride is a gastric pro-motility agent that was withdrawn or restricted in most countries because of evidence suggesting that it causes serious, sometimes fatal, ventricular arrhythmias [1]. The evidence for cisapride's arrhythmogenicity included a chemical structure similar to that of pro-arrhythmic agents [2], electrophysiological studies [3] and spontaneously reported adverse drug events [4]. In contrast, the largest controlled epidemiological study available at the time of withdrawal found an adjusted rate ratio of 1.0 [95% confidence interval (CI) 0.3, 3.7] for the association between current cisapride use and arrhythmic events [5]. A subsequent study found a rate ratio of 1.6 (95% CI 0.65, 3.82) for current cisapride use [6]. If one assumes based on electrophysiological studies, convincing case reports and other non-epidemiological evidence that cisapride can cause ventricular arrhythmias, it is reasonable to ask why this risk has not been confirmed in epidemiological studies. One potential explanation is that although the epidemiological studies have been large by conventional standards (approximately 9000 and 11 000 exposed person-years, respectively), they have still been too small to identify an increase over the low baseline incidence of ventricular arrhythmia, which is about 0.5 to two events per thousand person-years [5–9]. Indeed, insufficient study size could be a potential explanation given the statistically nonsignificant rate ratio of 1.6 from the second epidemiological study [6].

We sought to examine the potential association between cisapride and ventricular arrhythmia in an epidemiological study larger than those conducted previously. In addition to examining the overall association, we sought to characterize the dose–response relationship and potential associations with drugs that inhibit cisapride's metabolism.

Methods

Overview and study population

We performed a case–control study nested within a cohort of person-time exposed to cisapride, metoclopramide or a proton pump inhibitor (PPI) in a population of US Medicaid enrollees. Metoclopramide and PPIs were chosen as comparator drugs because they and cisapride are used for similar, albeit not identical, sets of indications. There are only very scant data suggesting a potential arrhythmogenic effect of metoclopramide: one experimental study showing an effect of intravenous administration on cardiac repolarization [10], and two published case reports of arrhythmias occurring in association with intravenous administration [11, 12]. We are unaware of any published data suggesting a potential association between PPIs and ventricular arrhythmia or sudden cardiac death. We considered PPIs as a group rather than individually. Because the database included many more PPI users than metoclopramide users, we randomly selected as many PPI users as there were metoclopramide users.

The data for this study came from the Medicaid programs of California, Florida, New York, Ohio and Pennsylvania from 1999 to 2000, which were obtained from the US Centers for Medicare and Medicaid Services (CMS) [13]. Medicaid is a series of state-run programmes with joint state and federal funding that provide medical and prescription coverage to low-income and specials needs individuals. Women, children and minorities are overrepresented in Medicaid compared with the general US population. These states comprise about 13 million Medicaid enrollees at any one time, or about 35% of the Medicaid population. The data consist of final-action claims that have undergone quality assurance review and editing by CMS. Because 15–17% of Medicaid beneficiaries are co-enrolled in Medicare [14], we also obtained Medicare data on all dually eligible persons in these states to ensure the complete capture of outcomes. A series of quality assurance analyses of the linked Medicaid and Medicare data were performed, the results of which suggested that the data are of high quality [15].

This study was approved by the University of Pennsylvania's Committee on Studies Involving Human Beings, which granted waivers of informed consent and of Health Insurance Portability and Accountability Act authorization. The funding sources of this study had no role in its design, conduct or interpretation.

Eligible person-time

We included all person-time of new and continuing use of a study drug beginning with filling a prescription and ending with the earliest of the days' supply field, 30 days, or filling a subsequent prescription for the same or a different study drug, or the appearance of a diagnosis code of interest (listed below) in any claim type for that enrollee. We assumed that each prescription lasted for a maximum of 30 days because Medicaid prescriptions for these drugs in these states tend to be dispensed in 30-day increments, as we confirmed by examining frequency distributions of the day's supply and the number of days between subsequent prescriptions for the same enrollee. Person-time defined by prescriptions for multiple study drugs filled on the same date was excluded. We performed secondary analyses (i) restricted to the first observed study drug prescription for each person, (ii) restricted to persons exposed to only one study drug (nonswitchers), (iii) excluding enrollees in Medicaid-managed care plans (because data for these persons may be incomplete), and (iv) excluding persons with cancer.

Identification of cases and medical record validation

An earlier study using Medicaid data showed that the positive predictive value (PPV) for hospitalization with a

principal or nonprincipal diagnosis code for ventricular arrhythmia or sudden cardiac death was 73% [16]. We therefore originally planned to use as our study outcome any hospitalization with a discharge diagnosis [coded in the International Classification of Diseases, 9th edn (ICD-9)] of paroxysmal ventricular tachycardia (427.1), ventricular fibrillation and flutter (427.4), ventricular fibrillation (427.41), ventricular flutter (427.42), cardiac arrest (427.5), sudden death (798), instantaneous death (798.1) or death occurring in <24 h from onset of symptoms, not otherwise explained (798.2). We re-examined the PPV of this outcome definition by requesting hospital medical records on a random sample of 164 such events identified in our study cohort. As described previously [17], 128 (78%) of the requested records were obtained. The validation definition was a witnessed sudden collapse with the person found unconscious or dead, with evidence that the person had been alive in the preceding 24 h, or evidenced cardiac arrest or ventricular arrhythmia [18]. The validation definition was met in 118 of the 126 records, for a PPV of 92% (95% CI 86, 96). However, only 23 (19%) of the validated events originated in the outpatient setting, with the remainder originating during the hospital course. When considering only hospitalizations in which the diagnosis of interest was the principal discharge diagnosis (ostensibly the diagnosis chiefly responsible for the admission), seven of seven met the validation definition, and all such events began prior to hospitalization. Thus, the PPV for a principal diagnosis of interest as an indicator of ventricular arrhythmia or sudden cardiac death originating outside of the hospital was 100%, with a an exact binomial lower 95% confidence limit of 59%. We therefore used this operational definition as the study outcome, considering only incident diagnoses of persons contributing eligible person-time.

Selection of controls

We used incidence density sampling [19] to randomly select up to 50 controls for each case from among eligible person-time (defined above). This was achieved via risk set sampling, in which controls were sampled from a cohort of persons at risk of the outcome at the time that each occurred. Thus, each control was required to have at least as much prior eligible person-time following the study prescription as its matched case. We did not match on any other factors. Utilization of such a sampling frame in a case–control study yields an OR that is an unbiased estimate of the rate ratio from the underlying cohort [19–21].

Ascertainment of exposure, dose and covariates

As described above, all study time was considered exposed to either cisapride, metoclopramide or a PPI. The exposure variable was therefore determined by the identity of the drug for the prescription that contributed the relevant person-time. Daily dose was calculated assuming that the prescription was consumed over the day's supply (if day's supply was missing, we assumed 30 days) and categorized as less than or equal to *vs.* greater than the defined daily dose (DDD) for that drug [22].

We defined three types of potential confounding variables: chronic diseases, defined as a diagnosis ever before the current study prescription; drug markers of chronic disease, defined as a prescription ever before the current study prescription; and current drugs, defined as a prescription in the 28 days prior to the current study prescription. Lists of specific diagnostic codes and drugs are available from the authors. Because 37% of spontaneously reported arrhythmic events reported in association with cisapride occurred in persons receiving a CYP3A4 inhibitor [4], we examined co-administration of CYP3A4 inhibitors. To distinguish effects of CYP3A4 inhibition on cisapride pharmacokinetics *vs.* direct arrhythmogenic effects of the drugs themselves, inhibitors without and with known or suspected arrhythmogenic effects were separately examined. We studied current use of the following non-arrhythmogenic CYP3A4 inhibitors: aprepitant, atazanavir, chloramphenicol, cimetidine, delavirdine, diltiazem, efavirenz, fluvoxamine, indinavir, lopinavir, mibefradil, mifepristone, nefazodone, nelfinavir, norfloxacin, ritonavir, saquinavir, troleandomycin and verapamil; and potentially arrhythmogenic CYP3A4 inhibitors: amiodarone, ciprofloxacin, clarithromycin, erythromycin, fluconazole, fluoxetine, itraconazole, ketoconazole, nicardipine, tamoxifen, telithromycin and voriconazole.

Statistical analysis

Incidence rates and 95% CIs were first calculated for the outcome of interest for each study drug. We next used conditional logistic regression to calculate minimally-adjusted ORs for the association of cisapride and metoclopramide with the study outcome, using PPIs as the reference category (except where otherwise stated), adjusting for continuous age, sex, race, state and nursing home residence. Other potential confounding factors were then evaluated individually and included in the fully adjusted model if introduction changed the ORs for cisapride or metoclopramide by ≥10%. Unless otherwise stated, ranges in parentheses are 95% CIs. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC, USA), except for the unconditional additive interaction models [23], which were performed using STATA version 10.0 (StataCorp LP, College Station, TX, USA). The latter models were fit using the macro aflogit by Tony Brady (Public Health Laboratory Service, Statistics Unit, London, UK). *P*-values for the differences in attributable fractions from the additive models were calculated based on a *t*-test with a bootstrap estimate for the standard error [24].

Results

Within person-time exposed to cisapride, metoclopramide or PPIs, 4385 incident occurrences of an inpatient or

Table 1

Characteristics of Medicaid beneficiaries filling prescriptions for prokinetic drugs and incidence rates for hospitalization with a principal diagnosis of ventricular arrhythmia or sudden cardiac death

	Cisapride	Metoclopramide	PPI
Users	98 961	195 199	195 199
Prescriptions	439 590	664 218	1 188 698
Person-years	27 385	36 602	83 576
Hospital admissions with a principal diagnosis of ventricular arrhythmia or sudden cardiac death	35	38	72
Incidence rate per thousand person-years (95% confidence interval)	1.28 (0.89, 1.78)	1.04 (0.73, 1.43)	0.86 (0.67, 1.08)
Unadjusted rate ratio (95% confidence interval)	1.49 (0.96, 2.25)	1.21 (0.79, 1.80)	reference
User-level variables			
Female sex	67 643 (68.35%)	133 107 (68.19%)	132 603 (67.93%)
Age in years			
<35	17 936 (18.12%)	53 356 (27.33%)	25 631 (13.13%)
35–44	10 656 (10.77%)	23 111 (11.84%)	29 559 (15.14%)
45–54	12 610 (12.74%)	24 655 (12.63%)	30 552 (15.65%)
55–64	14 359 (14.51%)	25 662 (13.15%)	30 495 (15.62%)
65–74	18 643 (18.84%)	30 606 (15.68%)	38 314 (19.63%)
≥75	24 757 (25.02%)	37 809 (19.37%)	40 648 (20.82%)
Race			
White	55 567 (56.15%)	94 271 (48.29%)	96 574 (49.47%)
Nonwhite	43 394 (43.85%)	100 928 (51.71%)	98 625 (50.53%)
Prescription-level variables			
Nursing home residence	139 572 (31.75%)	191 801 (28.88%)	143 395 (12.06%)
Diagnoses ever in past			
Alcohol abuse	5 826 (1.33%)	16 937 (2.55%)	51 310 (4.32%)
Anaemia	102 444 (23.30%)	217 997 (32.82%)	355 115 (29.87%)
Arrhythmia/conduction disorder	54 178 (12.32%)	122 116 (18.38%)	209 530 (17.63%)
Asthma/chronic obstructive pulmonary disease	101 999 (23.20%)	193 309 (29.10%)	379 437 (31.92%)
Cancer	52 623 (11.97%)	107 447 (16.18%)	212 096 (17.84%)
Cerebrovascular disease	76 764 (17.46%)	150 661 (22.68%)	193 128 (16.25%)
Constipation	44 473 (10.12%)	74 861 (11.27%)	105 761 (8.90%)
Coronary artery disease	93 658 (21.31%)	179 843 (27.08%)	371 727 (31.27%)
Cystoparesis	802 (0.18%)	1 662 (0.25%)	3 067 (0.26%)
Depression/bipolar disorder	80 795 (18.38%)	147 707 (22.24%)	325 760 (27.40%)
Diabetes mellitus	124 943 (28.42%)	231 526 (34.86%)	350 104 (29.45%)
Dyspepsia	22 079 (5.02%)	43 578 (6.56%)	99 969 (8.41%)

Table 1

Continued

	Cisapride	Metoclopramide	PPI
Gastro-oesophageal reflux disease	112 674 (25.63%)	177 913 (26.79%)	350 221 (29.46%)
Gastroparesis	13 920 (3.17%)	29 802 (4.49%)	13 271 (1.12%)
Human immunodeficiency virus/acquired immune deficiency syndrome	2 456 (0.56%)	15 668 (2.36%)	32 221 (2.71%)
Heart failure/cardiomyopathy	73 136 (16.64%)	153 231 (23.07%)	240 480 (20.23%)
Hiccup	393 (0.09%)	1 569 (0.24%)	1 125 (0.09%)
Hypercholesterolaemia	69 571 (15.83%)	135 741 (20.44%)	360 227 (30.30%)
Hypertension	172 111 (39.15%)	311 058 (46.83%)	648 374 (54.54%)
Hypothyroidism	47 371 (10.78%)	86 270 (12.99%)	170 336 (14.33%)
Kidney disease	57 245 (13.02%)	140 496 (21.15%)	194 181 (16.34%)
Liver disease	29 997 (6.82%)	85 308 (12.84%)	151 307 (12.73%)
Obesity	14 511 (3.30%)	34 691 (5.22%)	78 198 (6.58%)
Oesophageal varices	832 (0.19%)	2 459 (0.37%)	7 724 (0.65%)
Organic psychosis	52 454 (11.93%)	89 564 (13.48%)	103 693 (8.72%)
Peptic ulcer disease	38 889 (8.85%)	83 686 (12.60%)	198 882 (16.73%)
Pulmonary circulation disease	9 071 (2.06%)	21 885 (3.29%)	38 010 (3.20%)
Rheumatoid arthritis and other inflammatory polyarthropathies	35 449 (8.06%)	75 858 (11.42%)	201 580 (16.96%)
Schizophrenic disorders	20 343 (4.63%)	34 577 (5.21%)	70 965 (5.97%)
Smoking	7 857 (1.79%)	25 934 (3.90%)	62 235 (5.24%)
Substance abuse	10 710 (2.44%)	33 490 (5.04%)	93 499 (7.87%)
Valvular heart disease	27 999 (6.37%)	67 104 (10.10%)	141 613 (11.91%)
Drugs used ever in past			
Angiotensin-converting enzyme inhibitor/ angiotensin II receptor antagonist	106 974 (24.33%)	184 286 (27.74%)	378 680 (31.86%)
Adrenergic bronchodilator (inhaled and oral)	111 473 (25.36%)	192 561 (28.99%)	326 992 (27.51%)
Anorexiant/anti-obesity agent	570 (0.13%)	1 264 (0.19%)	2 181 (0.18%)
Antiadrenergic, centrally and peripherally acting, non-α_1 selective antagonists	19 492 (4.43%)	47 366 (7.13%)	52 625 (4.43%)
Antiarrhythmic, class I (oral; excluding phenytoin)	2 732 (0.62%)	5 349 (0.81%)	10 093 (0.85%)
Antiarrhythmic, class III (oral)	2 316 (0.53%)	6 263 (0.94%)	11 783 (0.99%)
Antidiabetic	103 861 (23.63%)	187 658 (28.25%)	251 484 (21.16%)
β-blocker (systemic)	61 359 (13.96%)	108 886 (16.39%)	267 476 (22.50%)
Calcium channel blocker (nonverapamil)	90 170 (20.51%)	157 642 (23.73%)	329 932 (27.76%)

Table 1

Continued

	Cisapride	Metoclopramide	PPI
Calcium channel blocker (verapamil)	13 678 (3.11%)	23 100 (3.48%)	51 715 (4.35%)
Corticosteroid (inhaled)	35 988 (8.19%)	60 441 (9.10%)	145 747 (12.26%)
Corticosteroid (oral)	50 080 (11.39%)	95 742 (14.41%)	199 186 (16.76%)
Digoxin	37 720 (8.58%)	68 127 (10.26%)	100 813 (8.48%)
Immunosuppressants used for organ transplantation	3 852 (0.88%)	6 757 (1.02%)	13 986 (1.18%)
Lipid-lowering agent	68 265 (15.53%)	114 025 (17.17%)	300 295 (25.26%)
Loop diuretic	96 809 (22.02%)	159 028 (23.94%)	266 335 (22.41%)
Nitrates	69 081 (15.71%)	115 606 (17.40%)	241 784 (20.34%)
Thiazide diuretic	50 192 (11.42%)	83 114 (12.51%)	216 486 (18.21%)
Thyroid hormone	52 646 (11.98%)	76 928 (11.58%)	134 393 (11.31%)
Vasodilators (non-nitrate)	3 734 (0.85%)	10 052 (1.51%)	12 195 (1.03%)
Warfarin	22 297 (5.07%)	40 961 (6.17%)	67 415 (5.67%)
Xanthine derivatives	19 141 (4.35%)	37 638 (5.67%)	68 370 (5.75%)
Drugs used currently			
Adrenergic bronchodilator (inhaled and oral; limited to agents known to prolong the QT interval)	75 569 (17.19%)	111 935 (16.85%)	184 178 (15.49%)
Amantadine/foscarnet	2 694 (0.61%)	3 004 (0.45%)	4 250 (0.36%)
Antiarrhythmic, class Ia	1 114 (0.25%)	2 168 (0.33%)	3 298 (0.28%)
Antiarrhythmic, classes Ib & Ic (limited to agents known to prolong the QT interval)	575 (0.13%)	726 (0.11%)	1 741 (0.15%)
Antiarrhythmic, class III (limited to agents known to prolong the QT interval)	2 005 (0.46%)	5 070 (0.76%)	9 058 (0.76%)
Antiemetic 5-hydroxytryptamine3 receptor antagonist	1 041 (0.24%)	3 997 (0.60%)	3 836 (0.32%)
Antipsychotic	63 644 (14.48%)	95 086 (14.32%)	160 536 (13.51%)
Aspirin	23 880 (5.43%)	31 836 (4.79%)	89 012 (7.49%)
Azole antifungal	6 210 (1.41%)	17 194 (2.59%)	29 473 (2.48%)
β-Blocker (systemic)	53 373 (12.14%)	82 163 (12.37%)	204 280 (17.19%)
Calcium channel blocker (limited to agents known to prolong the QT interval)	1 164 (0.26%)	1 402 (0.21%)	2 166 (0.18%)
Calcium channel blocker (nonverapamil)	78 989 (17.97%)	121 019 (18.22%)	255 950 (21.53%)
Calcium channel blocker (verapamil)	11 473 (2.61%)	16 395 (2.47%)	36 187 (3.04%)
Chloral hydrate	1 838 (0.42%)	1 680 (0.25%)	871 (0.07%)
Clindamycin	2 655 (0.60%)	4 378 (0.66%)	5 910 (0.50%)
Cyclic and related antidepressant	56 714 (12.90%)	98 883 (14.89%)	178 599 (15.02%)

Table 1

Continued

	Cisapride	Metoclopramide	PPI
Cyclooxygenase-2 inhibitor	35 162 (8.00%)	51 822 (7.80%)	193 740 (16.30%)
Droperidol	35 (0.01%)	63 (0.01%)	86 (0.01%)
Ephedrine/phenylpropanolamine/pseudoephedrine	23 623 (5.37%)	32 605 (4.91%)	66 227 (5.57%)
Epinephrine	551 (0.13%)	759 (0.11%)	1 203 (0.10%)
Famotidine	43 998 (10.01%)	73 228 (11.02%)	26 731 (2.25%)
Felbamate/fosphenytoin	266 (0.06%)	326 (0.05%)	181 (0.02%)
Hydroxychloroquine/chloroquine/mefloquine	1 774 (0.40%)	2 577 (0.39%)	7 973 (0.67%)
Hydroxyzine	15 219 (3.46%)	24 451 (3.68%)	44 465 (3.74%)
Loop diuretic	83 724 (19.05%)	119 929 (18.06%)	195 208 (16.42%)
Macrolide antibiotic	25 227 (5.74%)	41 445 (6.24%)	104 073 (8.76%)
Magnesium supplement	3 779 (0.86%)	4 313 (0.65%)	7 928 (0.67%)
Meperidine	1 093 (0.25%)	2 185 (0.33%)	2 574 (0.22%)
Methadone	808 (0.18%)	1 711 (0.26%)	2 674 (0.22%)
Nonsteroidal anti-inflammatory drug	50 925 (11.58%)	73 257 (11.03%)	176 145 (14.82%)
Octreotide	143 (0.03%)	357 (0.05%)	295 (0.02%)
Pentamidine	19 (0.00%)	79 (0.01%)	265 (0.02%)
Phentermine/sibutramine	22 (0.01%)	65 (0.01%)	95 (0.01%)
Potassium supplement	58 811 (13.38%)	86 008 (12.95%)	125 646 (10.57%)
Potassium-sparing diuretic	18 044 (4.10%)	28 903 (4.35%)	61 092 (5.14%)
Quinine	6 026 (1.37%)	11 785 (1.77%)	20 864 (1.76%)
Quinolone antibiotic	42 579 (9.69%)	71 950 (10.83%)	109 922 (9.25%)
Sildenafil	939 (0.21%)	1 273 (0.19%)	8 749 (0.74%)
Tacrolimus	788 (0.18%)	1 123 (0.17%)	3 565 (0.30%)
Tamoxifen	2 653 (0.60%)	3 569 (0.54%)	6 787 (0.57%)
Thiazide diuretic	38 549 (8.77%)	49 685 (7.48%)	137 765 (11.59%)
Tizanadine	1 747 (0.40%)	2 210 (0.33%)	3 143 (0.26%)
Trimethoprim-sulfamethoxazole	20 876 (4.75%)	37 736 (5.68%)	51 555 (4.34%)

Table 2

Characteristics of principal diagnosis inpatient sudden cardiac death and ventricular arrhythmia events

Total events	145
Events followed by death within 2 days*	29 (20%)
ICD-9 427.1 (paroxysmal ventricular tachycardia)	†
ICD-9 427.41 (ventricular fibrillation)	†
ICD-9 427.5 (cardiac arrest)	25 (86%)
Events not followed by death within 2 days*	116 (80%)
ICD-9 427.1 (paroxysmal ventricular tachycardia)	76 (66%)
ICD-9 427.41 (ventricular fibrillation)	13 (11%)
ICD-9 427.42 (ventricular flutter)	†
ICD-9 427.5 (cardiac arrest)	36 (31%)

*Totals may sum to >100% as persons may have experienced a different principally-diagnosed code of interest in both a Medicaid and Medicare claim.
†Omitted to ensure current Centers for Medicare & Medicaid Services (CMS) privacy guidelines are met.
ICD-9, International Classification of Diseases, 9th edn, diagnostic code.

outpatient diagnosis of sudden cardiac death or ventricular arrhythmia were identified. Of these, 1402 were inpatient diagnoses, of which 145 had the diagnosis of interest as the principal diagnosis. Table 1 shows the incidence rate of the study outcome among users of each study drug and describes the characteristics of the exposure groups. The overall incidence rate was about one per 1000 person-years. The unadjusted rate ratio for cisapride *vs.* PPIs was 1.49 (0.96, 2.25). Compared with cisapride and PPIs, metoclopramide users were more likely to be <35 years old, consistent with this drug's use in nausea and vomiting in pregnancy, and more likely to have cerebrovascular disease, diabetes mellitus and past exposure to an antidiabetic agent. The latter two are consistent with metoclopramide's use for diabetic gastroparesis. PPI users were less likely to be nursing home residents and more likely to have dyspepsia, hypertension and peptic ulcer disease; past exposure to angiotensin antihypertensives, β-blockers, calcium channel blockers and thiazide diuretics; and current exposure to aspirin, β-blockers, calcium channel blockers, cyclooxygenase-2 inhibitors, nonsteroidal anti-inflammatory drugs and thiazide diuretics. Overall, there were no striking differences among the exposure groups.

Table 2 further characterizes the 145 cases of the outcome of interest. All cases had principal inpatient diagnosis codes indicative of cardiac dysrhythmia or cardiac arrest (ICD-9 codes subclassified under 427) rather than codes indicative of unknown sudden death (ICD-9 codes subclassified under 798). Of the 20% of cases dying within 2 days of admission, most (86%) had a diagnosis of cardiac arrest. Of the 80% of cases not dying within 2 days of their event, two-thirds had a diagnosis of paroxysmal ventricular tachycardia.

Table 3 shows characteristics of cases and controls, as well as minimally and fully adjusted ORs for cisapride and metoclopramide *vs.* PPIs. Compared with PPIs, the minimally adjusted OR for cisapride was 1.65 (1.08, 2.51), and the fully adjusted OR was 2.10 (1.34, 3.28). Using metoclopramide as the referent, the fully adjusted OR for cisapride was 1.89 (1.15, 3.12). The fully adjusted OR restricted to the first-observed prescription for each drug for each subject was 7.85 (1.95, 31.60) for cisapride and 1.88 (0.54, 6.55) for metoclopramide. The fully adjusted OR in nonswitchers was 2.70 (1.32, 5.50) for cisapride and 1.48 (0.85, 2.58) for metoclopramide. Excluding persons in Medicaid-managed care plans, the fully adjusted OR was 2.92 (1.55, 5.49) for cisapride and 0.64 (0.30, 1.36) for metoclopramide. Excluding patients with cancer, the fully adjusted OR was 1.90 (1.13, 3.17) for cisapride and 1.22 (0.74, 2.00) for metoclopramide.

The fully adjusted OR for cisapride was 2.11 (1.28, 3.47) in women and 1.66 (0.79, 3.49) in men (*P*-value for difference = 0.60). The fully adjusted OR for cisapride was 1.69 (0.89, 3.23) in those <65 years old and 2.67 (1.45, 4.95) in those ≥65 years old (*P*-value for difference = 0.31).

The fully adjusted OR for >1 DDD of cisapride (>30 mg) *vs.* lower doses was 0.98 (0.50, 1.71). The fully adjusted OR for >1 DDD of metoclopramide (>30 mg) *vs.* lower doses was 1.26 (0.62, 2.58).

The OR for non-arrhythmogenic CYP3A4 inhibitors was 1.39 (0.49, 3.90) in cisapride users and 1.73 (0.82, 3.64) in PPI users (*P*-value for difference = 0.74). The OR for potentially arrhythmogenic CYP3A4 inhibitors was 3.79 (1.76, 8.15) in cisapride users and 3.47 (2.06, 5.83) in PPI users (*P*-value for difference = 0.85). In an unconditional additive logistic regression model [23], the attributable fraction due to non-arrhythmogenic CYP3A4 inhibitors was 3.5% (−3.0, 9.5) in cisapride users and 3.1% (−1.8, 7.5) in PPI users (*P*-value for difference = 0.908). The attributable fraction due to potentially arrhythmogenic CYP3A4 inhibitors was 16.9% (7.0, 25.7) in cisapride users and 10.3% (3.5, 16.7) in PPI users (*P*-value for difference = 0.267).

Discussion

These results suggest that, overall, cisapride is associated with an approximate doubling to tripling of the risk of hospitalization for ventricular arrhythmia and sudden cardiac death. However, cisapride was associated with a nearly eightfold risk in the initial prescription period. This is consistent with the observation that 61% of cases of QT prolongation and ventricular arrhythmia reported to the US Food and Drug Administration in association with cisapride occurred within 30 days of initiation of cisapride therapy [4]. This marked apparent reduction in risk after the first prescription suggests that many persons who are at highest risk of a drug-induced arrhythmia experience it early in therapy, leaving a relatively low-risk group remaining in the treatment pool. However, the risk remained approximately doubled even in later cisapride prescriptions.

Table 3

Selected characteristics of cases and controls, and results of multivariable models

	Cases *n* = 145 *n* (%)	Controls *n* = 7250 *n* (%)	Minimally adjusted odds ratio (95% confidence interval)*	Fully adjusted odds ratio (95% confidence interval)†
Study drug exposure				
Cisapride	35 (24.1)	1302 (18.0)	1.65 (1.08–2.51)	2.10 (1.34–3.28)
Metoclopramide	38 (26.2)	1820 (25.1)	1.24 (0.83–1.88)	1.11 (0.72–1.71)
Proton pump inhibitor	72 (49.7)	4128 (56.9)	reference	reference
Female sex	84 (57.9)	4987 (68.8)	0.57 (0.40–0.80)	0.62 (0.43–0.90)
Mean age in years (odds ratio per year)	63	59	1.02 (1.01–1.03)	0.99 (0.98–1.00)
Diagnoses ever in past				
Anemia	72 (49.7)	2014 (27.8)	2.61 (1.84–3.70)	–
Arrhythmia/conduction disorder	54 (37.2)	1123 (15.5)	3.15 (2.19–4.52)	–
Cerebrovascular disease	43 (29.7)	1168 (16.1)	2.19 (1.48–3.23)	–
Coronary artery disease	79 (54.5)	1959 (27)	3.26 (2.28–4.68)	1.39 (0.92–2.10)
Diabetes mellitus	77 (53.1)	2256 (31.1)	2.44 (1.73–3.43)	–
Gastroparesis	‡	144 (2)	2.63 (1.19–5.79)	–
Heart failure/cardiomyopathy	87 (60)	1366 (18.8)	7.25 (5.01–10.50)	3.17 (2.04–4.93)
Kidney disease	63 (43.4)	1140 (15.7)	4.09 (2.90–5.77)	2.62 (1.79–3.84)
Liver disease	30 (20.7)	796 (11)	2.19 (1.44–3.33)	–
Pulmonary circulation disease	11 (7.6)	199 (2.7)	2.76 (1.46, 5.25)	–
Valvular heart disease	49 (33.8)	729 (10.1)	4.42 (3.06, 6.38)	–
Drugs used ever in past				
Angiotensin-converting enzyme Inhibitor/ angiotensin II receptor antagonist	69 (47.6)	2144 (29.6)	2.10 (1.50, 2.96)	–
Antiarrhythmic, class III (oral)	12 (8.3)	56 (0.8)	10.49 (5.36, 20.52)	–
Digoxin	51 (35.2)	634 (8.7)	5.52 (3.77, 8.10)	2.65 (1.73, 4.07)
Immunosuppressants used for organ transplantation	‡	78 (1.1)	4.94 (2.07, 11.82)	–
Loop diuretic	70 (48.3)	1590 (21.9)	3.39 (2.38, 4.82)	–
Nitrates	53 (36.6)	1284 (17.7)	2.60 (1.81, 3.74)	–
Vasodilators (non-nitrate)	‡	77 (1.1)	4.10 (1.81, 9.28)	–
Warfarin	27 (18.6)	393 (5.4)	3.62 (2.32, 5.65)	–
Drugs used currently				
Antiarrhythmic, class III (limited to agents known to prolong the QT interval)	24 (16.6)	42 (0.6)	30.79 (17.33, 54.71)	15.16 (8.15, 28.19)
β-Blocker (systemic)	39 (26.9)	1100 (15.2)	2.06 (1.41, 3.01)	–
Loop diuretic	63 (43.4)	1198 (16.5)	4.10 (2.86, 5.88)	–
Magnesium supplement	‡	45 (0.6)	5.92 (2.40, 14.59)	–
Potassium supplement	35 (24.1)	825 (11.4)	2.30 (1.53, 3.45)	–

*Adjusted for age, sex, race, state, nursing home residence. †Adjusted for age, sex, race, state, nursing home residence, and potential confounders found to change the odds ratio for cisapride or metoclopramide by ≥10% (coronary artery disease, heart failure/cardiomyopathy, kidney disease, past digoxin use, current class III antiarrhythmic use). ‡Omitted to ensure current Centers for Medicare & Medicaid Services (CMS) privacy guidelines are met.

Note: while numerous other potential confounders were considered, for the sake of readability, this table above only reports those with a statistically significant odds ratio >2 in the minimally adjusted model.

Consistent with earlier studies [5, 6], women had a lower absolute risk, although the OR for cisapride was numerically but not statistically higher in women than in men. Similarly, the OR for cisapride was numerically but not statistically higher in those ≥65 years old *vs.* younger persons.

Contrary to expectation, our data did not support the existence of a dose–response relationship for cisapride. Furthermore, although the use of potentially arrhythmogenic CYP3A4 inhibitors was associated with an increased risk in cisapride users, their use was associated with a nearly identically increased risk in PPI users. This suggests a direct pharmacological effect of potentially arrhythmogenic CYP3A4 inhibitors rather than a drug–drug interaction with cisapride. This explanation is supported by the similar, nonsignificantly elevated ORs for non-arrhythmogenic CYP3A4 inhibitors in users of cisapride and of PPIs.

This study has limitations. An important limitation of any nonrandomized pharmacoepidemiological study is the potential for confounding by indication, i.e. that baseline differences among treatment groups may have affected the rates of the outcome of interest. We attempted to limit this potential by including comparator drugs with similar (albeit not identical) indications to cisapride, and by measuring and adjusting for a number of potential confounding factors. Indeed, adjustment for these factors strengthened rather than weakened the

association with cisapride. Nevertheless, we cannot rule out the possibility that unmeasured factors may have contributed to the observed association. Another limitation of population studies of drug-induced arrhythmia is potential error in outcome ascertainment. For example, because this study relied on hospital diagnoses, it would have missed fatal events that did not result in hospitalization. However, this would have introduced bias only if the probability of surviving to hospitalization varied by drug. Also, although the study outcome had a high PPV, the observed PPV was based on a small sample.

These results provide the first unequivocal epidemiological confirmation of the association between cisapride and occurrence of serious arrhythmias. Furthermore, they provide important information on the magnitude of the association, suggesting that cisapride is associated with an approximate doubling to tripling of risk overall and, importantly, a nearly eightfold risk in the initial prescription period. Our results do not support a dose–response relationship. Furthermore, although we found an association with potentially arrhythmogenic CYP3A4 inhibitors, this is more plausibly explained by a direct effect of these agents rather than by a true interaction with cisapride.

Competing interests

S.H. has served as a consultant to Johnson & Johnson and Wyeth on matters unrelated to the study drugs. He has also received research funding from Pfizer unrelated to this topic. S.E.K. has received grant funding from Pfizer, GlaxoSmithKline, and the Aetna Foundation, all unrelated to the topic of this manuscript, and has also served as a consultant to several pharmaceutical companies, including Pfizer, GlaxoSmithKline, and Centocor, all unrelated to the topic of this manuscript. W.B.B. has not consulted on the drugs under study (or competitor drugs), but has consulted for Johnson & Johnson, Wyeth-Ayerst, AstraZeneca, and Apotex, and has also received grant funds from Pfizer unrelated to this topic, although not as a principal investigator. This study was supported by grant R01HL076697 from the National Heart, Lung, and Blood Institute and by Cooperative Agreement U18HS010399 from the Agency for Healthcare Research and Quality. The funding sources had no role in the study's design, conduct or interpretation.

The authors thank Liu Qing, BS, Hopiy Kim, BS, Colleen M. Brensinger, MS and Jesse L. Chittams, MS for statistical programming, Gerrie Barosso RD, MPH, MS of the Research Data Assistance Center of the University of Minnesota for assistance in obtaining and using the data, and Kate Gelperin, MD, MPH for providing comments on the manuscript.

REFERENCES

1 Hirst C, Cook S, Dai W, Perez-Gutthann S, Andrews E. A call for international harmonization in therapeutic risk management. Pharmacoepidemiol Drug Saf 2006; 15: 839–49.

2 Levine A, Fogelman R, Sirota L, Zangen Z, Shamir R, Dinari G. QT interval in children and infants receiving cisapride. Pediatrics 1998; 101: E9.

3 Drolet B, Khalifa M, Daleau P, Hamelin BA, Turgeon J. Block of the rapid component of the delayed rectifier potassium current by the prokinetic agent cisapride underlies drug-related lengthening of the QT interval. Circulation 1998; 97: 204–10.

4 Wysowski DK, Corken A, Gallo-Torres H, Talarico L, Rodriguez EM. Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and Food and Drug Administration regulatory actions. Am J Gastroenterol 2001; 96: 1698–703.

5 Walker AM, Szneke P, Weatherby LB, Dicker LW, Lanza LL, Loughlin JE, Yee CL, Dreyer NA. The risk of serious cardiac arrhythmias among cisapride users in the United Kingdom and Canada. Am J Med 1999; 107: 356–62.

6 Enger C, Cali C, Walker AM. Serious ventricular arrhythmias among users of cisapride and other QT-prolonging agents in the United States. Pharmacoepidemiol Drug Saf 2002; 11: 477–86.

7 Zheng ZJ, Croft JB, Giles WH, Ayala CI, Greenlund KJ, Keenan NL, Neff L, Waltigney WA, Mensah GA. State-specific mortality from sudden cardiac death – United States, 1999. MMWR Morb Mortal Wkly Rep 2002; 51: 123–26.

8 Pratt CM, Hertz RP, Ellis BE, Crowell SP, Louv W, Moyé L. Risk of developing life-threatening ventricular arrhythmia associated with tefenadine in comparison with over-the-counter antihistamines, ibuprofen and clemastine. Am J Cardiol 1994; 73: 346–52.

9 Hennessy S, Bilker WB, Knauss JS, Margolis DJ, Kimmel SE, Reynolds RF, Glasser DB, Morrison MF, Strom BL. Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. BMJ 2002; 325: 1070.

10 Ellidokuz E, Kaya D. The effect of metoclopramide on QT dynamicity: double-blind, placebo-controlled, cross-over study in healthy male volunteers. Aliment Pharmacol Ther 2003; 18: 151–5.

11 Chou CC, Wu D. Torsade de pointes induced by metoclopramide in an elderly woman with preexisting complete left bundle branch block. Chang Gung Med J 2001; 24: 805–9.

12 Bentsen G, Stubhaug A. Cardiac arrest after intravenous metoclopramide – a case of five repeated injections of metoclopramide causing five episodes of cardiac arrest. Acta Anaesthesiol Scand 2002; 46: 908–10.

13 Hennessy S, Carson JL, Ray WA, Strom BL. Medicaid databasesed. In: Pharmacoepidemiology, 4th edn, ed. Strom BL. Chichester, UK: John Wiley and Sons, Inc., 2005; 281–94.

14 Medicare Payment Advisory Commission. Report to the Congress: New Approaches in Medicare. Washington, DC: Medicare Payment Advisory Commission, 2004.

15 Hennessy S, Leonard CE, Palumbo CM, Newcomb C, Bilker WB. Quality of Medicaid and Medicare data obtained through Centers for Medicare and Medicaid Services (CMS). Med Care 2007; 45: 1216–20.

16 Staffa JA, Jones JK, Gable CB, Verspeelt JP, Amery WK. Risk of selected serious cardiac events among new users of antihistamines. Clin Ther 1995; 17: 1062–77.

17 Hennessy S, Leonard CE, Bilker WB. Researchers and HIPAA. Epidemiology 2007; 18: 518.

18 Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. Arch Gen Psychiatry 2001; 58: 1161–7.

19 Flanders WD, Louv WC. The exposure odds ratio in nested case–control studies with competing risks. Am J Epidemiol 1986; 124: 684–92.

20 Lubin JH, Gail MH. Biased selection of controls for case–control analyses of cohort studies. Biometrics 1984; 40: 63–75.

21 Miettinen O. Estimability and estimation in case-referent studies. Am J Epidemiol 1976; 103: 226–35.

22 Wessling A, Boëthius G. Measurement of drug use in a defined population. Evaluation of the defined daily dose (DDD) methodology. Eur J Clin Pharmacol 1990; 39: 207–10.

23 Greenland S, Drescher K. Maximum likelihood estimation of the attributable fraction from logistic models. Biometrics 1993; 49: 865–72.

24 Efron B, Tibshirani RJ. An Introduction to the Bootstrap. Monographs on Statistics and Applied Probability, Vol. 57. London: Chapman and Hall, 1993.